STATUS OF CLAIMS

Claims 54-57 are pending

REMARKS

Applicant herein traverses and respectfully requests reconsideration of the rejection of the claims as cited in the above referenced Office Action in view of the remarks set forth below.

I. The rejection of claim 54 under 35 U.S.C. §112 first paragraph should be withdrawn

Claim 54 remains rejected under 35 U.S.C. § 112 first paragraph as not being enabled by the specification. In particular, the Examiner contends that the disclosure is allegedly enabling only for virus-like particles comprising VP1 and VP2 but not for virus-like particles comprising VP1 in the absence of VP2.

In response thereto, Applicant maintains that the application provides sufficient guide post to enable on skilled in the art to practice the full scope of claim 54. The enablement requirement embraces the implicit subordinate mandate that "the specification teach those in the art to make and use the invention without 'undue experimentation.' "*In re Vaeck*, 947 F.2d 488, 495 [20 USPQ2d 1438] (Fed. Cir. 1991), quoting *In re Wands*, 858 F.2d 731, 737 [8 USPQ2d 1400] (Fed. Cir. 1988).

Enablement may be shown in any of three ways. The claims may be expressly enabled, as by a working example in the specification, or by the incorporation by reference of a second reference teaching enablement. There is, however, no requirement for working examples, if the claims are otherwise enabled. In *re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970). The claims may, alternatively, be implicitly enabled if their support is such that one of ordinary skill would be able to practice the invention without undue experimentation. In *re Wands*, 8 U.S.P.q.2d 1400 (Fed.Cir. 1988).

Applicant respectfully submits that the specification of the present invention expressly enabled as illustrated by a working example in the specification. Contrary to the Examiner's allegation, the specification of the present invention discloses sufficient information that a person of skill in the art can make and use the invention without undue experimentation. In this regards, the specification discloses information regarding i) isolation of B19-DNA (page 8, lines 9-22); ii) subcloning of B19-DNA into a plasmid (page 8, lines 25-34); iii) subcloning of said plasmid into pUC7 (page 8, lines 36 to page 9, line 14); iv) cloning into baculovirus vector pAcYM1 (page 9 line 16-page 10, line 4). Altogether, these information provides enabling disclosure to a skilled artisan regarding the preparation of plasmid containing VP1.

In addition, page 10, lines 5-19 provide description relating to cotransfection followed by purification of said recombinant virus containing VP1 (AcB19VP1L) (page 10, line 21 to page 11, line 7). The section on "Biosynthesis of recombinant VP1" (page 11, lines 9-36) discloses preparation as well as verification for biosynthesis of recombinant VP1. Accordingly, this disclosure in the specification explicitly provides enablement for virus-like particles comprising VP1 in the absence of VP2.

Applicant also respectfully submits that a second reference teaching enablement has been incorporated in the present specification or that claim 54 is implicitly enabled because their support is such that one ordinary skilled in the art would be able to practice the invention without undue experimentation. That the priority document enables one to successfully express VP1 and VP2, individually and as a fusion protein is especially true considering that it was well known that the two protein VP1 and VP2 are expressed in a way part of the coding sequence of one is spliced when expressing the other. Thus, considering that the prior application provided the appropriate species sites and the complete open reading frame, it is not seen why one skilled in the art using known recombinant techniques could not have succeeded in expressing VP1 and VP2 as was later claimed.

The language in the priority application, as conceded by the Examiner in prior

Office Actions that the priority application specifically teaches "a vector containing one open reading from and splice sites for expression of both products from the open reading frame" should provide sufficient information to lead one skilled in the art to the expression of VP1 and VP2 individually and as fusion partners.

Applicant maintains her position that a skilled artisan armed with the information contained in the Dutch priority document, i.e., open reading frame and the appropriate splice site, could easily generate individual VP1 and VP2 proteins using recombinant DNA techniques known at the time. Considering that an applicant needs not teach what is well known to one skilled in the art, it will be our position that the Dutch priority document provides sufficient guideposts to enable one skilled in the art to express VP1 and VP2 such as to enable us to claim prior of the Dutch application. In fact, Applicant respectfully maintains that the absence of working examples in the priority application, as alleged by the Examiner, is not fatal to a finding of enablement as it relates to expression of VP1 and VP2. In this regard, note the Federal Court's instruction in *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1367, 231 USPQ 81 (Fed. Cir. 1986) that "[A] patent need not teach, and preferably omits, what is well known in the art.' In fact, "A patent applicant need not include in the specification that which is already well known to and available to the public." *Paperless Accounting, Inc. v Bay Area Rapid Transit Sys.*, 231 USPQ 649 (Fed. Cir. 1986).

Also, the Examiner's blanket nonenablement rejection is contrary to established patent law principles in that the Examiner has not provided any objective evidence to support his assertion. *Ex parte Balzarini*, 21 USPQ 2d 1899 (Pt. Bd. App. 1991). As a matter of law, therefore, the rejection is deficient and should be withdrawn.

Indeed, such blanket rejections, without objective argumentation to support them, have been criticized by both the Board of Appeals and the C.C.P.A. as improper. In *Ex parte Shing Change*, App. No. 88-2581, the Board stated:

"(I)n making a rejection for lack of enablement,

> it is incumbent upon the examiner to explain why the objective truth of the disclosure is doubted and to back up such assertions with acceptable objective evidence or reasoning in support thereof. Only in this manner does an applicant have a fair opportunity to overcome the examiner's doubts by submitting suitable proofs to indicate that the specification is indeed enabling."

See also *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1967), in which the CCPA stated:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which corresponds in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In the absence of objective evidence, Applicant respectfully requests the Examiner's rejection to be withdrawn.

II. The rejection of claim 55 as anticipated by Ozawa under 35 U.S.C. §102(b) may properly be withdrawn

In rejecting claim 55, the Examiner has taken the position that:

> Ozawa et al teaches B19 capsid proteins VP1 and VP2 which were isolated by synthesis using in vitro translation from an isolated synthetic mRNA, and purified by immunoprecipitation. See page 10923, second column, under "In vitro production of capsid proteins by synthetic B19 transcripts". These proteins meet each and every limitation of the claims.

It is well settled that each prior art reference, in order to constitute a bar

under section 102, must contain within its four corners all of the elements of the claimed invention found in substantially the same situation where they do substantially the same work in the same say. See, for example, the Federal Court's instruction in *Atlas Power Co. V. E.I. du Pont de Nemours and Co.*, 221 U.S.P.Q. 427, (N.D. Texas 1983), *aff'd*, 224 U.S.P.Q. 409, (Fed.Cir. 1984).

Claim 55 is drawn to the isolated and purified VP1 capsid protein of the human parvovirus B19. In sharp contrast, Ozawa reference is directed specifically to translation regulation of B19 parvovirus protein produced by multiple upstream AUG triplets. Although Ozawa et al expressed VP1 and VP2 capsid proteins of human parvovirus B19 in human erythroid bone marrow cells; this reference fails too specifically teach isolation and purification of VP1 and VP2 capsid proteins. The Examiner alleges that Ozawa purified VP1 and VP2 capsid proteins by immunoprecipitation which is not supported by the reference. In fact, Ozawa explicitly stated that immunoprecipitation is used solely for detection and demonstration (not isolation and purification):

> "To detect B19 specific proteins, immunoprecipitation was performed using a specific convalescent phase serum..." (page 10923, first column, under "In Vitro Translation)."
>
> "The authenticity of the proteins as B19 products was demonstrated by immunoprecipitation with a specific human antiserum..." (page 10923, second column, first paragraph)."

Because Ozawa fails to teach the isolation and purification of VP1 capsid protein of parvovirus B19, the reference does not contain within its four corners all of the elements of the claimed invention . In view of the above recitation, Applicant respectfully request that the 102 rejection be withdrawn.

III. The rejection of claims 54 and 57 under 35 U.S.C. 102 (e) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as

obvious over Young may properly be withdrawn.

The question concerning claims 54 and 57 is whether the recombinant virus-like particles consisting of VP1 and VP2 protein of human parvovirus B19, formed in Spodoptera frugiperda cells by the technique described in the present application, are identical to the (empty) capsids of the human parvovirus B19 formed in CHO cells by the technique described in Young et al (5,508,186). A skilled person in the art has good reason to conclude that the two kinds of particles are different.

First, in the Young reference, empty B19 parvovirus capsids are found in the nuclei and cytosol of the CHO cells transfected (column 5, lines 47-48). In contrast, the present inventor has never observed this in the nuclei of baculovirus infected insect cells. So, not only are the capsids described in Young produced in a totally different cellular environment, they are apparently formed in a different cell organelle, namely the nucleus as opposed to the cytoplasm.

Second, Young does not contain a description of the protein composition or the purity of the empty capsids, so we cannot make direct comparisons. However, Young's group in a later work "Self-assembled B19 parvovirus capsids, produced in a baculovirus system, are antigenically and immunogenically similar to native virions", Kajigagy et al., PNAS 88, 4646-4650 (1991) expressly states on page 4650, left column, lines 8-13:

> "The baculovirus capsids should be a suitable reagent for human vaccine trials, not only because they are easy to produce and purify, but also because, in contrast to 3-11-5 cell lysates, they lack the simian virus 40 enhancer-promoter element and are synthesized in untransformed cells."

Thus, they point to a material difference between the empty capsids produced in CHO cells according to Young and the virus-like particles consisting of VP1 and VP2 protein formed in *Spodoptera frugiperda* cells according to the present invention.

Also, continuing in lines 13-15, Young's group states:

"The ration of VP1 to VP2 in empty capsids is higher after coinfection of insect cells than in empty capsids produced by 3-11-5 cells."

This is amplified by Bansal et al., *Vaccines* **92** , 315-319 (1992), who explain on page 317 in the paragraph "Immunogenicity of Recombinant Parvovirus B19 Antigens", lines 11-16:

"As expected, the 3-11-5 and bac VP2 capsids failed to elicit antibodies specific for the capsid protein region unique to VP1, since these sequences are either severely underrepresented in the immunogen (3-11-5) or lacking altogether (bac VP2). However, significant antibody responses to the VP1 unique region were generated when this polypeptide was represented in the immunogen (as in bacVP1/bacVP2 and cro VP1-227)"

The reason for this becomes clear when reading point in the legend of Table 1 on page 318:

"The capsid particles produced by the late passage 3-11-5 cells used in this study contained only a trace level of VP1 protein".

From this it must be concluded that CHO-expressed capsids contain a decreasing amount of VP1 depending on passage number and cell line stability, which means they will always have a different ratio of VP1/VP2 compared to baculovirus-expressed capsids produced under standardized conditions. Accordingly, Young's reference cannot serve as a 102(e) reference. Applicant respectfully submits further that the product per se and not only the process for preparing it is novel, and thus claims 54 and 57 has novelty over Young's reference.

IV. The rejection of claims 55 and 56 as unpatentable over the combination of Wood et al with any of Sisk et al, Cotmore et al, Ozawa et al should be withdrawn.

The Examiner alleges that it would have been within the ordinary skill of the art to substitute known B19 VP2 or VP1 capsid proteins with reasonable expectation of success in obtaining a similarly antigenic product.

Applicant maintains that the claimed invention would not be obvious from the

teachings and disclosures of the following references, separately or in any proper combination, **absent** applicant's disclosure. The Examiner can only combine the disclosures of the cited references as basis for the proposed rejection of the claimed invention by way of **hindsight.** This is contrary to established principles of patent law.

The present invention involves native parvovirus B19 that has a capsid consisting of the two capsid proteins, VP1 and VP2. These capsid proteins have an isometric symmetry for which protein—protein interactions play an important role in contrast to capsids having a helicoidal capsid symmetry for which protein-nucleic acid interactions are decisive for the structure of the capsid particle. Isometrical capsids can be composed of identical copies of a single protein or of two or more different proteins. Where the capsid is composed of many different proteins, it may be likely, and expected, that the elimination of one of said proteins will not be detrimental to formation of capsid particles. In the case of human parvovirus B19, however, the capsid is composed of only two different proteins, VP1 and VP2. Prior to the instant applications, a person skilled in the art would have expected that the absence of one of these proteins would prevent the formation of capsid particles. In this respect, we note that the function of the proteins VP1 and VP2 in the parvovirus B19 capsid formation and stability was unknown at the priority date. In addition, there had not been any description of a formation of VP2 particles before the priority date.

A THE PRIOR ART, TAKEN AS A WHOLE, DOES NOT DISCLOSE OR SUGGEST THE FULL SCOPE OF THE CLAIMED INVENTION

Wood et al. disclose the expression of the canine parvovirus VP2 capsid protein and its use as a vaccine against canine parvovirus. Wood et al. is innocently silent with regard to human B19 capsid proteins. This reference alone, or in combination with the other references discussed below, fails to render obvious the subject matter of the present applications.

Accordingly, Wood et al. is irrelevant, because of the absence in this reference and other references, showing a close homology between canine and human

parvovirus. In fact, as noted in Chapman et al., (previously submitted to the Patent Office) there is reason to believe that the structures of canine parvovirus (CPV) and human parvovirus are different. This conclusion is further supported by Agbande et al. (also previously submitted) wherein the authors show a striking dissimilarity in the surface topology between FPV and B19, it being an art recognized fact that the FPV is almost identical to CPV (canine parvovirus).

Further support for the proposition that the B19 parvovirus and CPV are antigenically dissimilar, i.e., do not cross-react antigenically, is evident from Cotmore et al., who based their conclusion on DNA hybridization studies. Given that there is no cross—reaction antigenically between canine parvovirus and human B19 parvovirus, and that there is low sequence homology and low DNA homology between canine parvovirus and human B19 parvovirus, a skilled artisan would have no basis to extrapolate the work done by Wood et al. on the use of CPV as a vaccine to the expectation that B19 capsid proteins would be useful as vaccines, much less that they would be useful as diagnostic agents for reliably detecting B19 antibodies in human sera.

Accordingly, Applicant argues that the dissimilarity of the CPV to human B19 is sufficient to lead a skilled artisan away from the claimed invention, and especially from substituting human B19 with CPV, which would be the case if one were to follow the Examiner's suggested combination.

In view of the above teachings and further in view of Agbande and Chapman et al., it is unlikely that one skilled in the art would combine Wood et al. with any of Sisk, Cotmore, or Ozawa, when the resulting combination would invariably lead to a non workable capsid protein.

Not only would the skilled artisan be dissuaded from combining Wood et al. with any of the cited references, but when taken as a whole, it becomes evident that even if Wood et al. were so combined, the resulting protein would be inefficient and may not

have the proper conformational structure required for it to be efficiently recognized by the appropriate antibodies. Thus, Applicant maintains that when the combination of references is taken as a whole, not only would the result be an inoperational capsid protein, especially considering that the CPV is structurally different than human B19 but also that the combination would "teach away" from the claimed invention.

In addition, even assuming that such a combination were indeed proper, the argument is available that the claimed capsid proteins are highly immunogenic and antigenic as is evident from table I and II of the present invention. In sharp contrast, the protein resulting from the above combination would not be as **antigenic and immunogenic** as the capsid of the present invention.

The data in Tables 1 and 2 of the present application show that the VP1 and VP2 capsid proteins of the present invention gave no false positives and no false negatives when used to detect B19 antibodies in human sera. The above arguments are further supported by Brown et al, Virus Res., 15: 197-212 (1990), copy previously provided to the PTO. This reference shows no false negatives or false positives with respect to the claimed B19 proteins. Given the state of the prior art, it was surprising and unexpected that the VPI and VP2 capsid proteins of the present invention could provide this highly advantageous result.

When the references are viewed as a "whole", which they must be, the resulting combination will invariably yield a capsid protein that is structurally different than human B19 protein. Even if the combination were proper, the resulting protein would be far **inferior** to those of the present invention.

B. IN ADDITION, THE PROPOSED COMBINATION "TEACHES AWAY" FROM THE CLAIMED INVENTION

Sisk et al. teach expression of a fusion protein in *E.coli*. Sisk et al.'s fusion protein (196 kd) consisted of beta-galactosidase and a polypeptide encoded by the structural gene encoding capside proteins VP1 and VP2. Cotomore et al. describe

expression of a "tripartite" and a "bipartite" fusion protein in *E.coli*. The tripartite fusion protein comprises a B19 fragment (emphasis supplied) fused in between the lambda repressor protein and beta-galactosidase while in the bipartite fusion protein the beta galactosidase has been deleted. Again, there is no suggestion of either a VP1 or VP2 individually or as a fusion protein. Importantly, in both the tri- and bipartite fusion proteins, the B19 expressed is a fragment and not a whole protein. The authors also fail to express any unfused VP1 or VP2. While Ozawa directed specifically to expression of VP1 and VP2 capsid proteins of human parvovirus B19 in human erythroid bone marrow cells, this reference fails to specifically teach isolation and purification of VP1 and VP2 capsid proteins.

To the contrary of the Examiner's contention, Sisk et al. actually **teach away** from the use of recombinant unfused VP1 and/or VP2 capsid proteins by discussing the advantages of recombinant fusion proteins and the disadvantages of recombinant unfused proteins (page 107, right column, first paragraph under "DISCUSSION"):

> The B-galactosidase fusion protein produced by pWPS17.1 in E. coli was shown to be a reliable source of viral antigen for detection of B19 related antibodies in human serum. There have been numerous reports of using B-galactosidase fusion proteins as a source of antigen from a variety of different viruses. For Western blot analysis the resolution of high molecular weight fusion proteins in a region of the polyacrylamide gel devoid of other E. coli proteins is a distinct advantage. In addition, protein segments produced as B-galactosidase fusions are generally stable while the same segments unfused to B-galactosidase are often degraded in E. coli. The ability to construct prokaryotic fusion proteins is advantageous when the sole source of a viral antigen is the live virus. (Emphasis added).

Even if one were to combine the references as suggested by the Examiner, i.e., Sisk, the above observation **teaches away** from individual VP1 and VP2 proteins and their use in diagnostic assays, which is contrary to the claimed invention. In our opinion, this is sufficient to remove any motivation to combine the references of Wood et al. with Sisk et al. and Cotomore et al. In fact, all the three cited prior art references teach only the **fusion** expression of B19 capsid proteins, or segments thereof, as a fusion protein and **teaches away** from unfused VP1 and VP2 capsid protein.

There is serious doubt that canine parvovirus (Wood et al.) would be a suitable candidate that can be substituted with a human B19 parvovirus as clearly evident from Cotmore et al. that the B19 is only distantly related to other serotypes in this family. That Cotmore et al. (1986) is irrelevant to the present invention is confirmed by Sisk et al., at page 1079, right column, second paragraph under "DISCUSSION". In addressing Cotmore et al.'s major shortcoming, Sisk et al. note:

> The recent study by Cotmore et al. described the construction of two expression plasmids containing B19 viral DNA sequences encoding the non-structural and capsid proteins of the viral genome. These constructs expressed viral specific B-galactosidase hybrid proteins in E. coli. Rabbit antisera directed against the hybrid protein from the clone expressing nt 2897-3479 recognize both the 83 kD and 58 kD B19 capsid polypeptides in the plasma of acutely infected patients. . . . . However, it was not demonstrated that the expressed recombinant polypeptides produced from these clones could be used as a source of anticren to detect antibodies to parvovirus in the sera of infected patients or from the sera of asymptomatic individuals. (Emphasis added.)

Furthermore, one skilled in the art would have discarded the fusion protein taught by all these references (i.e., Sisk, Cotmore or Ozawa) as a possible diagnostic agent for detecting B19 antibodies.

In view of the above recitation, it is believed that the grounds for the above rejection are overcome.

V. The rejection of claims 54 and 57 under 35 U.S.C. 103 as being unpatenable over Kajigaya et al in view of French et al and any of Sisk et al, Cotmore et al, or Ozawa et al, should be withdrawn

The Examiner alleges that one skilled in the art would combine Kajigaya's reference with that of French and any of Sisk, Cotmore or Ozawa to obtain the claimed invention.

Applicant respectfully submits that it is not within the framework of 35 U.S.C.§ 103 to pick and choose from the relevant prior art only as much as will support a holding of obviousness, to the exclusion of other parts necessary to the full appreciation of what the prior art suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 230 U.S.P.Q. 416, 420 (CAFC 1986); *in re Wesslau*, 147 U.S.P.Q. 391 (CCPA 1965). In considering these references separately neither reference leads to the invention.

Obviousness cannot be established by combining pieces of prior arts absence some teaching, suggestion, or incentive supporting the combination. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q. 1276 (Fed. Cir. 1987). There is nothing in the prior art to lead a person of ordinary skill to the combination of these reference to recombinantly make VP2 protein (without fused with another protein). A skilled artisan has good reasons to conclude that the two expression systems (CHO cells disclosed by Kajigaya et al. vs the Spodoptera frugiperda cells described in the present applications are completely different. First, capsid proteins are produced in a totally different cellular environment in these system; namely, they are apparently formed in a different cell organelle---the nucleus (in CHO) as opposed to the cytoplasm (in Sf cells). Second, the ratio of VP1/VP2 as well as overall conformation are different. Indeed, a skilled artisan would recognize a material difference between two systems.

All of the three cited prior art references teach only the **fusion** expression of B19 capsid proteins, or segments thereof. There is nothing in these prior arts to lead a person of ordinary skill leading to combine French's reference to recombinantly make a B19 fusion protein; let along that the Sisk, Cotmore and Ozawa in fact **teach away** from unfused VP1 and VP2 capsid protein.

The rejection amounts to the application of a standard of "obvious to try" which has been repeatedly by many courts as improper ground for 35 U.S.C. § 103 rejection. Note the Federal Court's instruction in *The Gillette Co. V S.C. Johnson & Johnson Inc.*,

16 U.S.P.Q.2d 1923, 1928 (Fed.Cir. 1990). *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed.Cir. 1990), wherein the Court noted:

> As we recently explained,
> [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. The Gillette Co. V. S.C. Johnson & Johnson Inc., 16 USPQ2d 1923, 1928 (Fed.Cir. 1990). In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed.Cir. 1990).

In view of the foregoing recitation, regarding the absence of suggestion for combining the references, it is respectfully submitted that the Examiner's statement in support of her rejection is conclusory and the rejection represents a hindsight reconstruction and should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully submits that claims 2-8, 29-33, 40-44 and 52 are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at (212) 848 1046. The undersigned may also be contacted by email at erzucidlo@gu.com.

AUTHORIZATION

No fee is believed to be due with this amendment. The Commissioner is, however, authorized to charge any required fees which may be due, or credit any overpayment, to Deposit Account No. 07-1855, Order No. 35853.17

Respectfully submitted,

Date: August 7, 2000

By _____ 31,900
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